REMARKS

Amendments to the Claims

Claim 2 and Claim 6 have been canceled.

Claims 1, 3-5, 7-8 and 11-13 have been amended.

New Claims 14-21 have been added.

Claims 1, 3-5, 7-8 and 11 have been amended to clarify that the myelodysplastic syndrome treated is "TNFα-mediated" myelodysplastic syndrome. Support for these amendments is found in the specification, for example, at page 16, lines 15-18 and page 57, line 16 to page 59, line 14.

Claims 1, 5 and 11 have been further amended to recite that the administered antibody competitively inhibits binding of human TNFα to anti-TNFα chimeric monoclonal antibody cA2. Support for these amendments is found in the specification, for example, at page 19, lines 17-24.

Claim 1 has been further amended to recite that the antibody administered is a "TNFα-inhibiting amount of an anti-TNFα antibody." Support for this amendment to Claim 1 is found in the specification, for example, at page 19, lines 17-24.

Claim 3 has been further amended to recite "...administering to the human an effective TNFα-inhibiting amount of anti-TNFα chimeric monoclonal antibody cA2." Support for this amendment to Claim 3 is found in the specification, for example, at page 10, lines 8-15 and page 19, lines 17-24.

Claim 4 has been further amended to recite "...administering to the human at least one anti-TNFα chimeric monoclonal antibody cA2, or an antigen-binding fragment thereof." Support for this amendment to Claim 4 is found in the specification, for example, at page 10, lines 8-15; page 17, lines 2-8; and page 19, lines 17-24.

Claims 5 and 11 have been further amended to recite "...administering to the human an effective TNFα-inhibiting amount of an anti-TNFα chimeric antibody...." Support for these amendments is found in the specification, for example, at page 10, lines 8-15 and page 19, lines 17-24.

Claim 11 has been further amended to recite that the administered anti-TNFα chimeric antibody binds to a neutralizing epitope of human TNFα. Support for this amendment to Claim 11 is found in the specification, for example, at page 10, lines 8-15; page 16, lines 12-19; and

page 19, lines 7-24.

New Claim 12 is directed to the method of Claim 1 wherein said anti-TNFα antibody is a humanized antibody. Support for new Claim 12 is found in the specification, for example, at page 9, lines 8-11; page 19, lines 7-9; and originally-filed Claim 12.

New Claim 13 is directed to the method of Claim 1 wherein said anti-TNFα antibody is a human antibody. Support for new Claim 13 is found in the specification, for example, at page 9, lines 8-11; page 19, lines 7-9; and originally-filed Claim 13.

New Claim 14 is directed to the method of Claim 1 wherein said anti-TNFα antibody binds with high affinity to a neutralizing epitope of human TNFα. Support for new Claim 14 is found in the specification, for example, at page 10, lines 8-15; page 16, lines 12-19; and page 19, lines 7-24.

New Claim 15 is directed to the method of Claim 1 wherein said anti-TNFα antibody binds to a neutralizing epitope of human TNFα *in vivo* with an affinity of at least 1×10^8 liter/mole, measured as an association constant (Ka), as determined by Scatchard analysis. Support for new Claim 15 is found in the specification, for example, at page 10, lines 8-15; and Example X, particularly page 80, line 24 to page 81, line 12.

New Claim 16 is directed to the method of Claim 1 wherein said anti-TNFα antibody is administered to the human by means of parenteral administration. Support for new Claim 16 is found in the specification, for example, at page 59, lines 23-29.

New Claim 17 is directed to the method of Claim 1 wherein said anti-TNFα antibody is administered to the human by means of intravenous administration, subcutaneous administration or intramuscular administration. Support for new Claim 17 is found in the specification, for example, at page 59, lines 23-29.

New Claim 18 is directed to the method of Claim 1 wherein said anti-TNFα antibody is administered to the human orally. Support for new Claim 18 is found in the specification, for example, at page 59, lines 23-29.

New Claim 19 is directed to the method of Claim 1 wherein said TNFα-inhibiting amount of the anti-TNFα antibody comprises a single or divided dose of about 0.1 - 50 mg/kg. Support for new Claim 19 is found in the specification, for example, at page 60, lines 7-24.

New Claim 20 is directed to the method of Claim 19 wherein the single or divided dose is

selected from the group consisting of: about a 0.1 - 1 mg/kg dose, about a 1.0 - 5 mg/kg dose, about a 5 - 10 mg/kg dose and about a 10 - 20 mg/kg dose. Support for new Claim 20 is found in the specification, for example, at page 60, lines 7-24.

New Claim 21 is directed to the method of Claim 1 further comprising administering to the human an effective amount of a therapeutic agent selected from the group consisting of: radiotherapeutics, cytotoxic drugs, monoclonal antibodies, chimeric antibodies, antibody fragments, antibody regions, lymphokines, cytokines, hemopoietic growth factors and immunoglobulins. Support for new Claim 21 is found in the specification, for example, at page 62, lines 4-23 and page 63, lines 3-7.

No new matter has been added by the amendments. Therefore, entry of the amendments into the application is respectfully requested.

Amendments to the Specification

The Examiner states that the application is to be reviewed and all spelling, trademarks, and like errors corrected, and that the first line of the specification should be amended to update the status of the priority documents.

Applicants have amended the specification to comply with the requirement to indicate trademarks and to update the status of related applications. Applicants have also corrected typographical errors in the specification. Support for the typographical errors is found throughout the specification. No new matter has been added by the amendments. Therefore, entry of the amendments into the application is respectfully requested.

Correspondence Address

Please note that the undersigned Attorney has taken over responsibility for this application. A Notice of Change of Contact Attorney is being filed herewith.

Priority

The Examiner states that the filing date of the instant claims is deemed to be the filing date of priority application USSN 08/192,093, filed February 4, 1994. The Examiner further states that "[i]t does not appear that the priority applications filed previous to 2/4/94 provide

sufficient written description for treating myelodysplastic syndrome with cA2-specific antibodies."

Applicants respectfully disagree. The instant claims are entitled to claim the benefit of priority application USSN 07/670,827 (filed March 18, 1991). Priority application USSN 07/670,827 provides sufficient written description and enablement for treating TNFα-mediated human disease, including myelodysplastic syndrome. USSN 07/670,827 discloses that the "[h]igh affinity chimeric anti-TNFα mAbs of the present invention, which have potent TNFα neutralizing activity, including TNFα-neutralizing fragments thereof, are useful as therapeutic agents for TNFα-mediated human disease...." (page 10, lines 22-25)

In addition, the specification of this priority application teaches and enables treatment of a representative number of species of the genus "TNFα-mediated diseases" including "acute and chronic immune diseases" and "neoplastic disease" with the claimed antibodies. (See USSN 07/670,827 at page 39, line 20 to page 40, line 9 and page 10, line 22 to page 11, line 4)

Myelodysplastic syndrome is a TNFα-mediated disease. See Verhoef *et al.*, *Leukemia, 6*:1268-1272 (1992). Myelodysplastic syndrome is closely related to leukemia, an acute and chronic neoplastic disease of the immune system. In fact, as the disease progresses, it converts into leukemia. For a clear understanding of the definition of myelodysplastic syndrome, please see, for example, eMedicine, "Myelodysplastic Syndrome," Emmanuel C. Besa, M.D., http://www.emedicine.com/med/topic2695.htm (Hereinafter "Besa") (Submitted herein as Exhibit A). Given that myelodysplastic syndrome is closely related to, and leads to, leukemia, an acute and chronic neoplastic disease of the immune system, the priority application provides sufficient written description and enablement for treating myelodysplastic syndrome. Therefore, Applicants are entitled to priority to USSN 07/670,827 (filed March 18, 1991). This priority application has been properly referenced on page 1 of the specification in compliance with 35 U.S.C. § 120.

Further, at the very least, Applicant's are entitled to priority to March 18, 1992. Applicants note that the Examiner cited Applicants' own PCT application Le *et al.* (WO/16553) as prior art. As discussed below, to qualify as prior art, a reference must meet the requirement of enablement. The PCT application (WO 92/16553) was filed March 18, 1992 and published October 1, 1992 and it also claims the benefit of priority to the same U.S. priority application

(USSN 07/670,827) as the subject application. Furthermore, the PCT application is substantially identical to the corresponding U.S. priority application (USSN 07/853,606) of the subject application, which was filed on the same date as the PCT application (March 18, 1992).

Therefore, if Applicant's disclosure in the PCT application (WO 92/16553) is sufficient to qualify as prior art, then Applicants' disclosure in the March 18, 1992 U.S. priority application (USSN 07/853,606) is sufficient to support the claims, and the claims, at the very least, are entitled to the benefit of priority to the filing date of March 18, 1992.

Moreover, priority application USSN 07/943,852, which was filed September 11, 1992, provides additional support for the claimed methods of treating TNFα-mediated diseases. For instance, Example XIX, discloses the clinical effectiveness of treating a known TNFα-mediated disease, rheumatoid arthritis, by administering the recited anti-TNFα antibodies. Although there is not a specific example directed to TNFα-mediated myelodysplastic syndrome, the mechanism of treatment would be the same regardless of the TNFα-mediated disease. This disclosure provides even further support for a 1992 priority date for the claimed treatment methods.

Rejection to Claims 1, 3-5, and 11-13 Under 35 U.S.C. § 112, first paragraph

Claims 1, 3-5 and 11-13 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The Examiner states that:

> It is apparent that the cA2 antibody is required to practice the claimed invention. As a required element, it must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. If it is not so obtainable or available, the enablement requirements of 35 USC 112, first paragraph, may be satisfied by a deposit of the cell line/hybridoma which produces this antibody. See 37 CFR 1.801-1.809.

Applicants respectfully disagree. The cA2 antibodies can be obtained from publicly available material with only routine experimentation and a reliable screening test. Therefore, the biological materials for cA2 antibodies need not be, and have not been, publicly deposited.

Applicants direct the Examiner's attention to the Federal Circuit decision in *In re Wands*, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988) (a copy of which is attached as Exhibit B for the Examiner's convenience). The claims at issue in *In re Wands* recited methods for an immunoassay using high affinity monoclonal antibodies that the Appellants found to have unexpectedly high sensitivity and specificity. The position of the PTO was that the data showed that the production of the antibodies is unpredictable and unreliable, so that it would require undue experimentation for one skilled in the art to make them. However, the court in *In re Wands* disagreed, noting that "[e]nablement is not precluded by the necessity for some experimentation such as routine screening," as long as the experimentation was not undue. *Id.* at 1404. The court concluded that undue experimentation would not be required to practice the claimed invention.

The court first stated that "Wands' disclosure provides considerable direction and guidance on how to practice their invention and presents working examples." *Id.* at 1406. The court further stated that "[t]here was a high level of skill in the art at the time when the application was filed, and all of the methods needed to practice the invention were well known." *Id.* The court in *In re Wands* recognized that the nature of monoclonal antibody technology is such that it involves screening hybridomas to determine which ones secrete antibodies with desired characteristics, and that practitioners of this art are prepared to screen negative hybridomas in order to find one that makes the desired antibody. *Id.* The court went on to state that "in the monoclonal antibody art it appears that an 'experiment' is not simply the screening of a single hybridoma, but is rather the entire attempt to make a monoclonal antibody against a particular antigen." *Id.* at 1407.

In considering the factors enumerated in *In re Wands*, Applicants' disclosure provides considerable direction and guidance on how to practice their invention, and presents numerous working examples. For example, the sequences of the variable regions of the antibodies are disclosed in Figures 16A-16B. In addition, the specification teaches methods of producing the claimed cA2 antibodies according to the present invention (See instant Detailed Description at page 32, lines 7 through 24; page 34, line 10 through page 35, line 4; and Examples III-IX). Chimeric A2 (cA2) anti-TNFα antibody consists of the antigen binding variable regions of the high-affinity neutralizing mouse antihuman TNF IgGl antibody, designated A2, and the constant regions of a human IgGl, kappa immunoglobulin. The human IgGl Fc region improves

allogeneic antibody effector function, increases the circulating serum half-life, and decreases the immunogenicity of the antibody. The avidity and epitope specificity of the chimeric A2 is derived from the variable regions of the murine A2. Chimeric A2 neutralizes the cytotoxic effect of both natural and recombinant human TNF. (See, for example, instant Detailed Description at page 34, line 10 to page 35, line 4). Examples I-IX teach the production, characterization and expression of the cA2 antibody. Examples X-XII teach assays for screening the cA2 antibody.

Additionally, it teaches methods of cloning a polynucleotide encoding an anti-TNF variable or constant region. (See, for example, instant Detailed Description at page 28, line 3 through page 31, line 2). Furthermore, the instant specification teaches that preferred anti-TNF monoclonal antibodies include those which will competitively inhibit *in vivo* the binding to human TNFα of anti-TNFα murine monoclonal antibody A2, chimeric monoclonal antibody cA2, or an antibody having substantially the same specific binding characteristics, as well as fragments and regions thereof. (See, for example, page 19, lines 17-20). It also teaches preferred methods for determining monoclonal antibody specificity and affinity (See, for example, instant Specification at page 19, line 25 through page 20, line 2, and Examples X and XI). In addition, there was a high level of skill in the art at the time when the application was filed, and all of the methods needed to practice the invention were well known.

Thus, a person of skill in the art would not be subject to undue experimentation without a reasonable expectation of success in order to make and screen cA2 antibodies which would have these claimed elements.

A deposit is not required because the disclosure is sufficient to enable production of the claimed antibodies. No more is required. The Examiner has failed to present any evidence which suggests that anti-TNFα antibodies with the claimed specificity are unusually difficult to isolate. In addition, Applicants' written specification fully enables the practice of the claimed invention because the claimed cA2 antibodies can be made from readily available starting materials using methods that are well known in the art and taught in detail in the specification.

As discussed above, and as detailed in the specification, cA2 is derived from the A2 antibody. The A2 antibody was publicly available at least as of 1992. (See Declaration of Jan Vilcek, M.D., hereinafter "Vilcek Declaration" at ¶ 5)

Furthermore, as noted by the Examiner, the claims encompassing the cA2 antibody in the

related U.S. Patent No. 5,919,452 were determined to be enabled. As is clear from the prosecution history, no deposit was necessary to satisfy the enablement requirement. Moreover, Applicants' argument that claims reciting cA2 are enabled and a cA2 deposit is not required has also been found persuasive in other related U.S. Applications, including USSN 09/756,301, now U.S. Patent No. 6,790,444.

As discussed above, the instant Specification and figures, together with what was known and available in the art, provide ample teachings such that one of skill in the art would not be subject to undue experimentation in order to make or use the claimed antibodies. Thus, the skilled artisan is enabled to make and use the claimed invention commensurate in scope with the claims. Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection to Claims 1-13 Under 35 U.S.C. § 112, first paragraph

The Examiner has rejected Claims 1-13 under 35 U.S.C. § 112, first paragraph, "because the specification, while being enabling for the 'TNFα-specificity'; does not reasonably provide enablement for any 'TNF-specificity' having such specificities."

Applicants respectfully disagree. As noted above, Applicants have canceled Claims 2 and 6. Further, to expedite prosecution, Applicants have amended Claims 1, 3-5, 7-8 and 11-13 to recite that the claimed antibodies are anti-TNFα antibodies. In the specification, Applicants have exemplified that the cA2 antibody competitively inhibits and binds with high affinity a neutralizing epitope of human TNF-α. Therefore, particularly as amended, the claims are enabled.

However, it should also be noted that anti-TNFα antibodies are not the only antibodies supported by the specification. As indicated in the specification, the present invention provides anti-TNF compounds and compositions comprising anti-TNF antibodies (Abs) and/or anti-TNF peptides which inhibit and/or neutralize TNF biological activity *in vitro, in situ* and/or *in vivo*, as specific for association with neutralizing epitopes of human tumor necrosis factor-alpha (hTNFα) and/or human tumor necrosis factor β (hTNFβ). (Page 16, lines 15-19.) Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection to Claims 1, 3-5 and 11-13 Under 35 U.S.C. § 112, second paragraph

The Examiner has rejected Claims 1, 3-5, and 11-13 as indefinite in the use of "cA2". Specifically, the Examiner states that "the use of 'cA2' antibody as the sole means of identifying the claimed antibody renders the claim indefinite because 'cA2' is merely a laboratory designation which does not clearly define the claimed product, since different laboratories may use the same laboratory designation [ ] to define completely distinct hybridomas / cell lines."

Applicants respectfully traverse this rejection. cA2 is not used as the sole means of identifying the antibody in the claims. The claims and specification provide a great deal of description regarding cA2's structure and properties. As amended, the claims explicitly state that the antibody is a chimeric anti-TNFα monoclonal antibody. Further, the specification clearly discloses that the antibody is a chimeric anti-TNFα monoclonal antibody, and provides a detailed disclosure of the production, structure and function of cA2. (Specification at page 17, lines 2-8; page 19, lines 7-16; page 26, lines 21-28 and page 34, line 12 to page 35, line 4) For instance, Examples I-IX teach the production, characterization and expression of the cA2 antibody and Examples X-XII teach assays for screening the cA2 antibody for specificity and efficacy.

Moreover, "cA2" is recognized by those skilled in the art as a unique identifier of Applicants' chimeric anti-TNFα monoclonal antibody. A number of scientific articles and press releases refer to Applicants' claimed monoclonal antibody as "cA2." (See, for example, Elliott, M. J. *et al.*, "Treatment of Rheumatoid Arthritis with Chimeric Monoclonal Antibodies to Tumor Necrosis Factor α," *Arthritis Rheum, 36*:1681-1690 (1993) (Exhibit C); Walker, R.E., "Inhibition of Immunoreactive Tumor Necrosis Factor-alpha by a Chimeric Antibody in Patients Infected with Human Immunodeficiency Virus Type 1," J. *Infect. Dis., 174*(1):63-8 (1996), abstract from AIDSLINEMED/96261994 (Exhibit D); and "New Monoclonal Antibody Effective Treatment For Crohn's Disease Therapy," Doctor's Guide (May 13, 1997), http://www.docguide.com/dg.nsf/PrintPrint/815D53A771190A4285256496004B0796 (Exhibit E)). These references are representative of the general knowledge of one skilled in the art and demonstrate that the identifier "cA2" clearly defines the claimed product. Thus, the cA2 antibody is well known in the art.

Moreover, a number of claims have issued which refer to the instant chimeric anti-TNFα monoclonal antibody as cA2. For example, the claims of related U.S. Patent No. 6,284,471,

which has the same priority date and has a substantially identical specification as the instant application, recite cA2. (A copy of the claim set of U.S. Patent No. 6,284,471 is attached hereto as "Exhibit F" for the Examiner's convenience).

Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection to Claims 1-13 Under 35 U.S.C. § 103(a)

The Examiner has rejected Claims 1-13 as being unpatentable over Verhoef *et al.*, *Leukemia, 6*:1268-1272 (1992) in view of Le et al. (WO 92/16553). The Examiner states that "...it would have been obvious to a person of ordinary skill in the art at the time the invention was made to apply the teachings of Le *et al.* to those of Verhoef *et al.* to obtain antagonistic TNF-α-specific antibodies, including those with the cA2 specificity, to counter the negative effects of TNF-α in myelodysplastic syndrome." Applicants respectfully disagree.

1. Le *et al.* and Verhoef *et al.* are not prior art

First, Applicants note that the Examiner has cited Applicants' own PCT application, Le *et al.* (WO 92/16553), as prior art. Le *et al.* (WO 92/16553) is not prior art under 35 U.S.C. § 102 (a) or § 102 (e) because the publication is not "by another." The inventors listed in Le *et al.* (WO 92/16553) are identical to the inventors of the subject application. In addition, Le *et al.* (WO 92/16553) is not prior art under 35 U.S.C. § 102 (b) because it was not published more than one year before Applicants' priority date. Specifically, as indicated above, Applicants are entitled to priority to U.S. Application Serial No. 07/670,827 (filed March 18, 1991). The PCT application (WO 92/16553) was filed March 18, 1992 and published October 1, 1992 and it also claims the benefit of priority to the same U.S. priority application (U.S. Serial No. 07/670,827) as the subject application. Furthermore, the PCT application is substantially identical to the corresponding U.S. priority application (U.S. Serial No. 07/853,606) of the subject application, which was filed on the same date as the PCT application (March 18, 1992).

To qualify as prior art, a reference must meet the requirement of enablement. As stated in the MPEP at § 2121.01:

"In determining that quantum of prior art disclosure which is necessary to declare an

> applicant's invention 'not novel' or 'anticipated' within section 102, the stated test is whether a reference contains an 'enabling disclosure'...."

(Quoting *In re Hoeksema*, 399 F.2d 269, 158 USPQ 596 (CCPA 1968).

> The disclosure in an assertedly anticipating reference must provide an enabling disclosure of the desired subject matter; mere naming or description of the subject matter is insufficient, if it cannot be produced without undue experimentation.

(Citing *Elan Pharm. Inc. v. Mayo Foundation for Medical and Education Research*, 346 F.3d 1051, 1054, 68 USPQ2d 1373, 1376 (Fed. Cir. 2003).

Therefore, if Le *et al. 's* disclosure, in the PCT application (WO 92/16553), is sufficient to qualify as prior art, then Applicants' March 18, 1992 priority application is sufficient to support the claims, and the claims, at the very least, are entitled to the benefit of priority to the filing date of March 18, 1992. Hence, Applicants' PCT application Le *et al.* (WO 92/16553) is not prior art.

Furthermore, as stated above, the priority date of the subject application (March 18, 1991) precedes the publication date of the Verhoef *et al.* reference cited by the Examiner. Therefore, Verhoef *et al.* is not prior art. In addition, Verhoef *et al.* does not teach Applicants' claimed antibodies. Verhoef *et al.* merely hypothesizes that "therapeutic intervention with inhibitors of TNF-α... may be, at least partly, an effective treatment for the anemia in MDS." (Verhoef *et al.* page 1271, col. 2) Thus, even if Verhoef *et al.* were prior art, Verhoef *et al.* does not describe or suggest Applicants' anti-TNFα antibodies, does not provide a reasonable expectation of achieving such antibodies having reduced immunogenicity and a therapeutic benefit, and does not reasonably suggest that the unexpected and superior results achieved and described herein were possible.

2. Prior to the data presented in Applicants' application, it was not reasonable to believe that a substantial clinical benefit was possible with a chimeric anti-TNF-α antibody

At the time of filing of the patent application, which claims the benefit of priority to U.S. Application Serial No. 07/670,827 (filed March 18, 1991), it was not known that chimerization of murine antibodies could be done successfully, or that chimeric antibodies provided superior results to murine antibodies for *in vivo* therapy. Further, the use of chimeric antibodies does not

eliminate the immunogenic reaction. The presence of non-human sequences in humanized and chimeric antibodies indicates that immunogenicity would still be a concern in therapies involving such antibodies. In fact, most (if not all) chimeric antibodies, similar to murine antibodies, generate an immune response in the administered animal. Thus, it was unclear, prior to the data presented by Applicants, that substantial clinical benefit was possible with a chimeric anti-TNFα antibody.

In fact, the art at the time of the claimed invention taught away from the concept that chimerization prevents an immunologic response against administered antibodies. For example, Brüggemann, M. *et al.*, "The Immunogenicity of Chimeric Antibodies," *J. Exp. Med.* *170*:2153-2157 (1989) (Exhibit G) tested allogeneic responses in mice to administered antibodies and found that in a chimeric derivative (in which only the V region frameworks were foreign), an immunologic response to the V region remained and was unattenuated, demonstrating to the authors that "foreign VH frameworks can be sufficient to lead to a strong antiantibody response." See page 2157. Further, the authors caution that even with wholly human antibodies, problems may be encountered with allogeneic responses directed against both the V and C regions. *Id.* at 2156.

Thus, the Brüggemann *et al.* reference further demonstrates unpredictability of clinical administration of chimeric antibody molecules. The authors state in the abstract, "...little is known about the immunogenicity of chimeric antibodies. It is unclear to what extent a particular V domain is characteristic of the species from which it originates, and therefore, whether a response will be elicited by an antibody in which only the V region is foreign." Abstract at 2153. This unpredictability must be considered when determining whether there was sufficient motivation for one of skill in the art to invent the claimed compounds.

The Brüggemann *et al.* reference teaches that it may not be sufficient in a clinical setting, in any meaningful way, to avoid the adverse immune response. Therefore, it teaches away from the use of chimeric antibodies as therapeutic compounds for clinical use, because it teaches that the administration of such antibodies can still lead to a strong immunological response in the patient, thereby rendering such administration clinically inadequate. One of skill in the art would not be motivated to invent a compound intended for a clinical administration which could do more harm to the patient (e.g., due to causing an adverse immune response) than good (due to

causing a therapeutic effect). In any event, these references would not motivate one of skill to modify a murine antibody with an expectation of achieving a clinically relevant improvement.

3. There is objective evidence of non-obviousness

Further, even assuming, *arguendo*, that a *prima facie* case of obviousness exists, which it does not, it would be overcome by the objective evidence of nonobviousness. Objective evidence of nonobviousness must be considered, as stated in the MPEP at § 2141:

> Objective evidence or secondary considerations such as unexpected results, commercial success, long felt need, failure of others, copying by others, licensing, and skepticism of experts are relevant to the issue of obviousness and must be considered in every case in which they are present. When evidence of any of these secondary considerations is submitted, the examiner must evaluate the evidence.

The claimed invention has led to unexpected results in relation to the prior art, and has satisfied a long-felt need in the relevant field. The fact that others in the field had tried for years to achieve a result, yet had failed, is evidence that the invention would not have been obvious to those skilled in the art when it was invented.

The claimed compounds have been shown to have unexpected results in terms of the degree of success in clinical studies, particularly in studies involving patients with long-term refractory TNFα-mediated disease. See Elliott, M. J. *et al.*, "Treatment of Rheumatoid Arthritis with Chimeric Monoclonal Antibodies to Tumor Necrosis Factor α," *Arthritis Rheum, 36*:1681-1690 (1993) (Exhibit C) (hereinafter "Elliott"). The magnitude of these results in the treatment of a TNFα-mediated disease could not have been reasonably predicted from the prior art. As noted in Elliott on page 1688, due to multiple and overlapping effects of cytokines such as IL-1 and TNFα and the fact that cytokines induce production of other cytokines and of themselves, there had been pessimism about whether targeting a single cytokine *in vivo* would have any beneficial effect. *See also*, Trentham, D. M., "Immunotherapy and Other Novel Therapies," *Curr. Opin. Rheumatol., 3*:369-372, 370 (1991) (Exhibit H) ("...the relevance of tumor necrosis factor and the biological outcome of its banishment by a monospecific inhibitor remain in doubt..."); and *Id.* at 371 ("Unidimensional attacks on aberrant immune pathways

might have a limited effect on the underlying disease process"). This initial skepticism as to the merits of the invention by experts in the field further establishes the nonobviousness of this invention. MPEP § 2141.

Neither Le *et al.* nor Verhoef *et al.* are prior art. Even if Verhoef *et al.* were prior art, Verhoef *et al.* does not describe or suggest Applicants' chimeric anti-TNF antibodies, does not provide a reasonable expectation of achieving such antibodies having reduced immunogenicity and a therapeutic benefit, and does not reasonably suggest that the unexpected and superior results achieved and described herein were possible. Moreover, the claimed invention has led to unexpected results and clearly satisfies a long felt but unsatisfied need. Thus, reconsideration and withdrawal of the rejection are respectfully requested.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

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